REMARKS

In the Action, claims 1-34 are rejected. In response, claims 1, 7, 10, 12, 13 and 20 are amended. The pending claims in this application are claims 1-34, with claims 1, 10 and 23 being independent. In view of these amendments and the following comments, reconsideration and allowance are requested.

Claims 1, 7, 10, 12, 13 and 20 are amended to clarify certain aspects of the invention and are not made to avoid the cited art. Although these amendments are unnecessary, they are being made to clarify the features of the invention as discussed below.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 3, 8, 9, 10, 12, 18 and 19 are rejected as being anticipated under 35 U.S.C. § 102(b) over U.S. Patent No. 5,935,942 to Zeimer. The rejection is based on the position that Zeimer discloses methods and materials for chemically treating a target site using fluorescent dyes that are encapsulated in liposomes, and thus, anticipates the claims.

It is well settled that anticipation of a claim requires that each and every limitation of the claim be found in a single prior art reference. The Action refers generally to two and a half pages of the Zeimer patent, but has not identified each of the claim limitations. Therefore, the Action has not established anticipation of the claims.

The present invention is directed to a method of hyperthermally treating tissue at a temperature that causes cell damage and kills at least some of the cells in the tissue of the target site. Claim 1 is specifically directed to a method of hyperthermally treating tissue by introducing a heat sensitive liposome containing a fluorescent dye where the dye is released at a temperature of at least 41°C and applying a heat source to the target site "to hyperthermally treat the tissue" and to release the dye. Claim 1 further recites the step of

fluorescing and visualizing the dye, thereby providing an indicator that a predetermined temperature has been attained that is sufficient to hyperthermally treat the tissue and kill cells in the tissue. Zeimer clearly fails to disclose each of these claimed steps.

As noted in the Action, Zeimer is directed to a method for chemically treating a target site. Zeimer does not hyperthermally treat the tissue. Zeimer uses the liposomes as a carrier for the treating agent, which is released in the target site so that the treating agent is able to chemically treat the target site. The temperature of the treatment of Zeimer is selected to release the chemical treating agent without damaging the tissue. Furthermore, Zeimer does not disclose heating the target site to hyperthermally treat the target site for a time sufficient to kill cells in the tissue. Therefore, Zeimer does not disclose or suggest these features of claim 1.

As noted in the Action, Zeimer is directed to the non-invasive heating of the tissue without causing thermal damage to the tissue. This is in direct contrast to the claimed invention which specifically recites the step of applying a heat source to the target site to hyperthermally treat the target site for a sufficient time to kill cells in the tissue. Thus, Zeimer specifically teaches away from the claimed invention. Accordingly, claim 1 is not anticipated by Zeimer.

Claim 3 depends from claim 1 to recite that the fluorescent dye is releasable from the liposomes at a temperature that is sufficient to kill cells in the tissue without denaturing proteins in the tissue. As noted above, Zeimer specifically heats the tissue in a manner to avoid damaging the cells or the tissue. Thus, Zeimer does not disclose a fluorescent dye releasable from liposomes at a temperature that is sufficient to kill cells in the tissue as recited in claim 3. Accordingly, claim 3 is not anticipated by Zeimer.

Claim 8 depends from claim 1 to recite that the heat source is a laser, microwave, infrared or ultrasonic source. Claim 9 depends from claim 1 to recite that the heat source is a heated fluid source. The Action refers generally to column 3 through column 7 of Zeimer. The Action has not identified where Zeimer discloses a heated fluid source for heating the target site and it is not seen where Zeimer discloses this step. Accordingly, claims 8 and 9 are not anticipated by Zeimer.

Independent claim 10 is directed to a method of detecting a threshold temperature and hyperthermally treating tissue in an animal. The method as recited in claim 10 introduces a first heat-sensitive liposome containing a first fluorescent dye into the animal to flow through the target site where the fluorescent dye is releasable at a temperature of at least 41°C, and heating the target site to a temperature to release the dye and fluorescing the dye to indicate and visualize a tissue temperature of at least 41°C. Claim 10 further recites the step of continuing heating the target site at a temperature of at least 41°C for a time sufficient to hyperthermally treat the tissue and kill cells in the tissue. Zeimer does not disclose or suggest releasing a fluorescent dye from heat-sensitive liposomes to indicate a minimum temperature of the tissue in the target site as recited in claim 10. Moreover, Zeimer does not disclose continuing heating the target site at a temperature of at least 41°C for sufficient time to hyperthermally treat the tissue and kill cells in the tissue. As noted above and as acknowledged in the Office Action, Zeimer specifically avoids thermal damage to the tissue and relies solely on the chemical treatment using the chemical agent released from the liposomes. Since Zeimer does not disclose hyperthermally treating the tissue, heating the tissue for sufficient time to kill cells in the tissue or releasing the fluorescent dye as an indicator that a minimum temperature is attained to hyperthermally treat the tissue, claim 10 is not anticipated by Zeimer.

Claim 12 depends from claim 10 to recite the step of heating the tissue to a temperature to kill cells in the tissue and at a temperature below the denaturing temperature. As noted above, Zeimer does not disclose or suggest heating the tissue to a temperature and for a time sufficient to kill cells in the tissue and where the temperature is below the protein denaturing temperature. Accordingly, claim 12 is not anticipated by Zeimer.

Claims 18 and 19 correspond to claims 8 and 9 except for depending from independent claim 10. For the reasons discussed in connection with claims 8 and 9, claims 18 and 19 are also not anticipated by Zeimer.

In view of the above comments, claims 1, 3, 8, 9, 10, 12, 18 and 19 are not anticipated by Zeimer.

Rejection Under 35 U.S.C. § 103(a)

Claims 2, 4-7, 11, 13-17 and 20-34 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,935,942 to Zeimer in view of U.S. Patent No. 5,976,502 to Khoobehi et al. Zeimer is cited as in the previous rejection as disclosing a method for chemically treating a target site using fluorescent dyes and tissue reactor substances without causing thermal damage to the tissue. Zeimer is further cited for disclosing the step of coadministering a fluorescent dye and a tissue reactive agent. The Action incorrectly contends that Zeimer is deficient only in failing to disclose first and second fluorescent dyes enclosed in liposomes. Khoobehi et al. is cited for disclosing a method of observing blood flow through the eye by injecting liposomes and blood cells containing the dye into the blood stream which can contain a single dye or a mixture of different dyes. The Action contends that it would be obvious to one of ordinary skill in the art to use either a single fluorescent

dye or a mixture of different fluorescent dyes as disclosed in Khoobehi et al. within the methods of Zeimer.

Khoobehi et al. does not provide the deficiencies of Zeimer such that the combination of Zeimer and Khoobehi et al. does not render the claims obvious. As noted above, Zeimer is directed to a method of chemically treating tissue in a non-invasive manner. Zeimer specifically applies the laser to the target site to prevent tissue damage. As disclosed in column 7, lines 58-65 of Zeimer, the non-invasive heating releases the contents of the liposomes "without causing substantial damage to the vasculature or extra vascular interstitial tissue". Therefore, Zeimer does not disclose the basic concept of the claimed invention of heating the tissue to a temperature and for a time sufficient to hyperthermally treat the tissue and kill cells in the tissue. Khoobehi et al. clearly fails to disclose hyperthermally treating tissue. Therefore, the combination of Khoobehi et al. with Zeimer does not render the claims obvious.

Claim 2 depends from claim 1 to specifically recite that the fluorescent dye is releasable from the liposome at a temperature of at least 42°C. The Action contends that the temperature is an obvious matter of choice. This contention is clearly incorrect and contrary to the present record. As disclosed on page 10, paragraph 32 of the specification, heating the tissue to a temperature of at least 42°C ensures that a sufficient temperature is obtained to thermally treat the tissue. It is known in the art that a temperature of 42°C causes cell damage. Zeimer specifically heats the liposomes at a temperature of 41°C to avoid damaging the tissue. Since Zeimer is specifically directed to a method of releasing the chemical treating agent without causing thermal damage, it is not obvious to one of ordinary skill in the art to increase the temperature of Zeimer. Increasing the temperature of Zeimer as suggested in the Action is contrary to the teachings of Zeimer. Therefore, the Action is incorrect in

stating that heating the tissue to a temperature of at least 42°C is an obvious matter of design choice in view of Zeimer. Zeimer effectively teaches away from heating the tissue to a temperature of at least 42°C and clearly provides no motivation or incentive to do so. Therefore, claim 2 is not obvious over Zeimer either alone or in combination with Khoobehi et al.

Claims 4 and 5 also depend from claim 1 and recite the step of heating the liposomes to release the bioactive compound at a temperature of at least 42°C. Claims 6 and 7 depend from claim 4 to recite the specific bioactive compound. For the reasons discussed in connection with claim 2, Zeimer clearly fails to disclose or suggest heating the tissue and the liposomes to a temperature of at least 42°C. Since heating the tissue to a temperature of 42°C is known to cause tissue damage, it is not obvious to one of ordinary skill in the art to modify Zeimer in a manner that is specifically contrary to the teachings and intent of Zeimer. Accordingly, claims 4-7 are not obvious over Zeimer either alone or in combination with Khoobehi et al.

Claim 11 depends from claim 10 to specifically recite heating the target site to a temperature of at least 42°C. As discussed above, heating tissue to a temperature of 42°C is known to cause tissue damage. Since Zeimer is specifically directed to a method of preventing thermal damage, it is not obvious to one of ordinary skill in the art to modify Zeimer as suggested in the Action. It is not an obvious matter of choice as suggested in the Action to modify Zeimer in a manner contrary to the specific teachings of Zeimer. Accordingly, claim 11 is not obvious over Zeimer either alone or in combination with Khoobehi et al.

Claims 13-17 depend directly or indirectly from claim 10 and also recite the step of heating the target site to a temperature of at least 42°C. For the reasons discussed in

connection with claim 11, it is not obvious to one of ordinary skill in the art to modify Zeimer as suggested in the Action to heat the tissue to a temperature of at least 42°C. Furthermore, it is also not obvious to one of ordinary skill in the art to modify Zeimer to heat the target site to a temperature range of 42°C to 50°C for one to 10 minutes as in claim 13 to hyperthermally treat the tissue without causing denaturization of the proteins in the tissue. Accordingly, claims 13-17 are also not obvious over Zeimer either standing alone or in combination with Khoobehi et al.

Claim 20 depends from claim 10 to recite the step of introducing a second encapsulated fluorescent dye where the dye is releasable from the liposome at a temperature of at least 50°C. Claim 20 further recites the step of visualizing and detecting the second fluorescent dye that is released from the second liposomes and reducing the temperature of the tissue to a temperature below 50°C in response to the detected second dye. The invention recited in claim 20 is specifically directed to providing an indicator in the form of the second dye that indicates that a temperature of the tissue has been attained that causes protein denaturization. Claim 20 also specifically recites the step of reducing the temperature in response to the indication of the second dye, thereby reducing the temperature below the protein denaturization temperature. Thus, the invention of claim 20 provides a first dye to provide an indication that the temperature sufficient for hyperthermally treating the tissue has been attained while also providing an indicator that the temperature is below the protein denaturization temperature. Thus, the combination of the first and second dyes provide an indication that the temperature of the tissue is maintained within a specific temperature range. Zeimer, either alone or in combination with Khoobehi et al., do not suggest the claimed method of maintaining the temperature within a specific temperature range.

As noted in the Action, Khoobehi et al. discloses the general concept of introducing more than one dye into the blood stream. However, Khoobehi et al. clearly fails to disclose a method of introducing a first liposome containing a dye as an indicator of the minimum desired treating temperature and a second liposome containing a dye to provide an indicator of the maximum desired treating temperature. Furthermore, Khoobehi et al. provides no motivation or incentive to modify Zeimer to provide liposomes to indicate that the tissue has attained a specific temperature range that is well above the maximum temperature sought by Zeimer to prevent thermal damage of the tissue. Accordingly, it is not obvious to one of ordinary skill in the art to modify Zeimer as suggested in the Action. In view of the above, claim 20 is not obvious over the combination of Zeimer and Khoobehi et al.

Claim 21 depends from claim 20 to recite that the cited fluorescent dye is released at a temperature where a protein denaturization occurs and the step of reducing the temperature of the tissue below the protein denaturization temperature in response to the second dye being detected. Khoobehi et al. clearly fails to disclose the use of the second dye that is released at a temperature where protein denaturization occurs and reducing the temperature of the tissue below the protein denaturization temperature. Claim 22 depends from claim 20 and also recites the step of heating the target site to a temperature below the protein denaturization temperature and below the release temperature of the second fluorescent dye. Zeimer and Khoobehi et al. clearly fail to disclose heating the tissue to a temperature below the release temperature of a dye encapsulated in a liposome. Accordingly, claims 21 and 22 are not obvious over the combination of Zeimer and Khoobehi et al.

Independent claim 23 is directed to a method of hyperthermally treating tissue by introducing a first liposome that releases a dye at a temperature of at least 42°C and a second liposome that releases a second dye at a temperature of at least 50°C. Claim 23 further recites

the step of heating the target site to a temperature of at least 42°C to release and fluoresce the first dye as an indication of an effective temperature for hyperthermally treating the tissue without releasing the dye from the second liposomes. As noted above, Zeimer and Khoobehi et al. both apply the laser to the liposomes to release the dye without causing thermal damage of the cells. Zeimer and Khoobehi et al. specifically avoid a temperature that causes thermal damage. In contrast, claim 23 specifically recites heating the tissue to a temperature of at least 42°C to hyperthermally treat the tissue.

Zeimer and Khoobehi et al. also fail to disclose or suggest a method of introducing a second liposome containing a dye and heating the tissue to a temperature below the temperature at which the second dye is released. Khoobehi et al. provides no motivation or incentive to one of ordinary skill in the art to use a second dye in a second liposome that is not released during the hyperthermal treatment. Accordingly, claim 23 is not obvious over the combination of Zeimer and Khoobehi et al.

Claim 24 depends from claim 23 to recite the step of detecting the second fluorescent dye and reducing the temperature of the tissue below the protein denaturization temperature of the tissue. Zeimer and Khoobehi et al. clearly fail to disclose or suggest reducing the temperature of the tissue in response to the detection of a dye. Accordingly, claim 24 is not obvious over the combination of Zeimer and Khoobehi et al.

Claims 25-34 are also allowable as depending from an allowable base claim and for reciting additional features that are not disclosed or suggested in the art of record. For example, the cited art does not disclose the use of different colored dyes as in claim 25, the phospholipids of claims 26 and 27, or the specific bioactive compounds of claims 28-31, either alone or in combination with the features of claim 23. Accordingly, these claims are not obvious over the art of record.

Claim 32 depends from claim 23 to recite that the first liposomes release the dye at a temperature of about 42-50°C. Thus, claim 32 recites the use of liposomes that rupture and release the dye in a temperature range that is effective for hyperthermally treating the tissue without causing protein denaturization. Zeimer and Khoobehi et al. do not disclose or suggest a liposome that ruptures at a temperature above the minimum temperature required for hyperthermal treatment and below the protein denaturization temperature. Claim 33 depends from claim 23 to recite that the first liposomes rupture and release the dye at a temperature of about 45°C to about 49°C. As noted above, tissue damage occurs at temperatures above 42°C and Zeimer and Khoobehi et al. specifically select liposomes that rupture below the temperature at which cell damage begins to occur. Zeimer and Khoobehi et al. provide no motivation or incentive to use a liposome that ruptures at a temperature of 45°C which is at a temperature that will cause tissue damage. Claim 34 depends from claim 23 to recite that the second liposomes rupture and release the dye at a temperature of about 50°C to 60°C. This temperature is well above the temperature at which tissue damage occurs and is above the temperature in which protein denaturization occurs. Zeimer and Khoobehi et al. provide no motivation of using a liposome that ruptures above the protein denaturization temperature. Accordingly, claims 32-34 are not obvious over the combination of Zeimer and Khoobehi et al.

In view of the deficiencies of Zeimer and Khoobehi et al., claims 1-34 are not anticipated by or obvious over Zeimer, either alone or in combination with Khoobehi et al. Accordingly, reconsideration and allowance are requested.

Respectfully submitted,

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